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Acromegaly and cancer risk: a cohort study in Sweden and Denmark

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Abstract

Objective: Several studies have suggested that patients with acromegaly have an increased risk of benign and malignant neoplasms, especially of the colon. To further investigate this relationship we evaluated cancer risk in population-based cohorts of acromegaly patients in Sweden and Denmark.

Methods: Nationwide registry-based cohorts of patients hospitalized for acromegaly (Denmark 1977–1993; Sweden 1965–1993) were linked to tumor registry data for up to 15–28 years of follow-up, respectively. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) were calculated to estimate cancer risk among 1634 patients with acromegaly.

Results: The patterns of cancer risk in Sweden and Denmark were similar. After excluding the first year of follow-up, 177 patients with acromegaly had a diagnosis of cancer compared with an expected number of 116.5 (SIR = 1.5, 95% CI = 1.3–1.8). Increased risks were found for digestive system cancers (SIR = 2.1, 95% CI = 1.6–2.7), notably of the small intestine (SIR = 6.0, 95% CI = 1.2–17.4), colon (SIR = 2.6, 95% CI = 1.6–3.8), and rectum (SIR = 2.5, 95% CI = 1.3–4.2). Risks were also elevated for cancers of the brain (SIR = 2.7, 95% CI = 1.2–5.0), thyroid (SIR = 3.7, 95% CI = 1.8–10.9), kidney (SIR = 3.2, 95% CI = 1.6–5.5), and bone (SIR = 13.8, 95% CI = 1.7–50.0).

Conclusions: The increased risk for several cancer sites among acromegaly patients may be due to the elevated proliferative and anti-apoptotic activity associated with increased circulating levels of insulin-like growth factor-1 (IGF-1). Pituitary irradiation given to some patients may have contributed to the excess risks of brain tumors and thyroid cancer. Our findings indicate the need for close medical surveillance of patients with acromegaly, and further studies of the IGF-1 system in the etiology of various cancers.

Introduction

Acromegaly is a rare and distinctive overgrowth syndrome resulting from excessive growth hormone (GH) secreted by benign pituitary adenomas or rarely hyperplasias. The clinical and biochemical effects of GH are mediated mainly by stimulating the production of insulin-like growth factor-1 (IGF-1, formerly called somatomedin-C) in the liver and other tissues [1]. Several previous studies of acromegaly have pointed to an increased risk of colonic polyps [2, 3] and cancer [4–9], and possibly other neoplasms [10]. Interest in these observations has been piqued by recent epidemiologic studies indicating that circulating level of IGF-1 may predict the risk of several common cancers [11–15]. To further investigate the cancer risks associated with acromegaly, we linked data from nationwide registry-based cohorts of patients hospitalized for acromegaly in Sweden and Denmark to their respective national cancer registries.

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Materials and methods

Methods used for studying cohorts of hospitalized patients in Sweden and Denmark have been reported previously [16] and are briefly summarized here. Using the centralized Danish Hospital Discharge Register and Swedish Inpatient Hospital Register, we identified patients hospitalized for acromegaly in Denmark during 1977–1989 (Danish ICD 8th revision discharge diagnosis code 253.00) and in Sweden during 1965–1993 (Swedish ICD 7th revision discharge diagnosis code 272.00, 8th revision codes 253.00 and 253.01, and 9th revision code 253A). Each record in these registries includes the patient's unique identification number, gender, date of birth, dates of hospital admission and discharge, discharge diagnoses, and surgical procedures. Patients with multiple admissions during the study periods had multiple records. To obtain follow-up information, the individual hospitalization records were linked to the Population, Migration, Cancer, and Causes of Death Registries through 1993 in each country.

All patients hospitalized with acromegaly were identified as initially eligible for study, but to minimize selection biases we excluded the first year of follow-up after diagnosis of acromegaly. In Denmark 463 patients were identified. Of these, 14 died in the hospital during their first admission with acromegaly, and 28 in the first year afterwards, leaving 421 for analysis. In Sweden we identified 1411 hospital records with unique registration numbers, but 66 had incomplete or non-matching (to the population registry) identification numbers, three had inconsistent gender information, and one had an invalid date of death. Thirty-three patients died during their first hospital admission, and another 95 patients died in the first year after diagnosis. After these exclusions, 1213 Swedish patients were eligible for further analysis.

Follow-up was accomplished through linkage to cancer registries in each country, beginning with diagnosis of acromegaly during the study period and continuing until the date of each subject's death or emigration, or until the end of follow-up (31 December, 1993), whichever occurred first. Second primary cancers were included in the analysis. Endocrine tumors in Sweden were excluded from the analysis, since all the observed tumors were benign pituitary adenomas. Person-years and cancers diagnosed in the first year of follow-up were excluded.

The expected number of cancers in each cohort was calculated by multiplying the number of person-years by the appropriate national, gender-, age-, calendar year-, and site-specific cancer incidence rates for each five-year age group and calendar year of observation. Risks of cancer were estimated by computing the standardized incidence ratios (SIRs), defined as the observed-to-expected number of cancers for all acromegaly patients combined, and by gender, age, and years of follow-up. The 95% confidence intervals (CI) were computed assuming that the observed number follows a Poisson distribution [17].

Results

The 1213 Swedish and 421 Danish patients with acromegaly provided 11,335 and 3389 person-years of follow-up, respectively. The mean follow-up time was 10.3 years in Sweden and 9.0 years in Denmark (Table 1). A total of 177 patients with acromegaly (136 in Sweden and 41 in Denmark) had a subsequent diagnosis of cancer, compared with 116.5 expected, yielding an SIR of 1.5 (95% CI = 1.3–1.8) (Table 2). Risks were increased for all digestive cancers (SIR = 2.1, 95% CI = 1.6–2.7), especially of the small intestine (SIR = 6.0, 95% CI = 1.2–17.4), colon (SIR = 2.6, 95% CI = 1.6–3.8), and rectum (SIR = 2.5, 95% CI = 1.3–4.2). All three small intestine cancers were malignant carcinoid tumors. The excess risk of colon cancer was distributed across all subsites (ascending colon SIR = 2.2; transverse SIR = 3.5; descending SIR = 3.3; sigmoid SIR = 3.5). Risk was also increased for kidney cancers (SIR = 3.2, 95% CI = 1.6–5.5), with 11 of 12 tumors being renal cell carcinomas.

Elevated risks were seen also for tumors (benign and malignant combined) of the brain and nervous system (SIR = 2.7, 95% CI = 1.2–5.0). The nine tumors comprised three meningiomas, one astrocytoma, one malignant neurinoma, and four tumors not otherwise specified (NOS). The risk of thyroid cancer was increased (SIR = 3.7, 95% CI = 1.8–10.9), based on three adenocarcinomas. The risk of bone cancer was also increased based on two cases (SIR = 13.8, 95% CI = 1.7–50.0), one arising from the skull and one from the long bones.

Non-significant increases in risk were seen for breast cancer (SIR = 1.3, 95% CI = 0.8–1.9), especially among

Table 1. Descriptive characteristics of acromegaly cohorts

	Sweden (n = 1213)	Denmark (n = 421)
Mean years of follow-up	10.3	9.0
Mean age at entry	50.4	51.6
Mean age at cancer	64.6	65.3
Mean age at exit	60.7	60.7
Mean year of entry	1980.2	1981.8
Percentage male	44.8	48.2
Person-years	11,335	3389

Table 2. Cancer incidence among acromegaly patients in Sweden and Denmark

Type of malignancy (ICD-7)	Sweden (11,335 person-years)				Denmark (3389 person-years)				Total (14,724 person-years)			
	Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95% CI
All cancers (140–209)[a,b]	136	83.7	1.6	1.4–1.9	41	32.8	1.3	0.9–1.7	177	116.5	1.5	1.3–1.8
Digestive system (150–159)	44	20.6	2.1	1.6–2.9	15	7.1	2.1	1.2–3.5	59	27.7	2.1	1.6–2.7
Stomach (151)	6	3.5	1.7	0.6–3.7	0	0.9	0.0	0.0–4.1	6	4.4	1.4	0.5–3.0
Small intestine (152)	3	0.4	7.1	1.4–20.6	0	0.1	0.0	0.0–47.6	3	0.5	6.0	1.2–17.4
Colon (153)	16	6.5	2.5	1.4–4.0	7	2.5	2.8	1.1–5.7	23	9.0	2.6	1.6–3.8
Rectum (154)	7	3.8	1.8	0.7–3.8	6	1.5	4.1	1.5–9.0	13	5.3	2.5	1.3–4.2
Liver (155.0)	2	1.0	2.1	0.2–7.5	1	0.3	3.3	0.0–18.5	3	1.3	2.4	0.5–6.9
Gall bladder (155.1)	2	1.0	2.0	0.2–7.2	0	0.1	0.0	0.0–30.5	2	1.1	1.8	0.2–6.4
Pancreas (157)	7	2.7	2.6	1.0–5.3	1	0.9	1.1	0.0–8.2	8	3.6	2.2	0.9–4.3
Lung (162)	10	6.2	1.6	0.8–3.0	4	4.6	0.9	0.2–2.2	14	10.8	1.3	0.7–2.2
Breast (170)	19	12.5	1.5	0.9–2.4	1	3.5	0.3	0.0–1.6	20	15.9	1.3	0.8–1.9
Corpus uterus (172)	3	2.9	1.0	0.2–3.0	1	0.9	1.2	0.0–6.4	4	3.8	1.1	0.3–2.7
Cervix (171)	3	1.3	2.4	0.5–7.0	0	0.6	0.0	0.0–6.1	3	1.9	1.6	0.3–4.7
Ovary (175)	2	2.7	0.7	0.1–2.6	0	0.7	0.0	0.0–4.9	2	3.5	0.6	0.1–2.1
Prostate (177)	12	8.5	1.4	0.7–2.5	1	1.8	0.6	0.0–3.1	13	10.3	1.3	0.8–2.2
Kidney (180)	10	2.9	3.5	1.7–6.4	2	0.9	2.2	0.3–8.1	12	3.8	3.2	1.6–5.5
Bladder (181)	3	4.0	0.8	0.2–2.2	0	2.0	0.0	0.0–1.8	3	6.0	0.5	0.1–1.5
Melanoma (190)	3	2.5	1.2	0.2–3.5	0	0.7	0.0	0.0–5.8	3	3.2	0.9	0.2–2.7
Non-melanoma (191)[c]	4	2.8	1.5	0.4–3.7	6	4.6	1.3	0.5–2.9	10	7.3	1.4	0.7–7.5
Brain and CNS (193)[d]	8	2.6	3.1	1.3–6.1	1	0.8	1.2	0.0–6.9	9	3.4	2.7	1.2–5.0
Thyroid (194)	3	0.7	4.3	0.8–12.6	0	0.1	0.0	0.0–33.4	3	0.8	3.7	1.8–10.9
Bone (196)	0	0.1	0.0	0.0–30.7	2	0.0	78.9	8.9–284.7	2	0.1	13.8	1.7–50.0
Connective tissue (197)	1	0.6	1.8	0.0–9.9	1	0.1	11.3	0.2–62.7	2	0.7	3.1	0.4–11.1
Hematopoietic (200–207)	7	6.0	1.2	0.5–2.4	2	1.8	1.1	0.1–4.0	9	7.8	1.2	0.5–2.2
Lymphoma (200–202)	5	2.9	1.7	0.6–4.0	1	0.8	1.3	0.0–7.0	6	3.7	1.6	0.6–3.6
Non-Hodgkin's lymphoma (200, 202)	4	2.5	1.6	0.4–4.1	1	0.7	1.5	0.0–8.2	5	3.2	1.6	0.5–3.7
All leukemia (204–207)	2	1.9	1.1	0.1–3.9	1	0.7	1.4	0.0–8.0	3	2.6	1.2	0.2–3.4

[a] Excluding 99 observed pituitary adenomas and the expected value for endocrine tumors in Sweden.
[b] Includes one esophagus, and three unspecified (Sweden), one lip, one other female genital, and three unspecified (Denmark).
[c] Includes squamous carcinoma in Sweden, and both squamous and basal cell carcinoma in Denmark.
[d] Includes benign and malignant tumors both in Sweden and Denmark.

women younger than age 50 (SIR = 2.3, 95% CI = 0.7–5.4). The risk of prostate cancer was also slightly elevated (SIR = 1.3, 95% CI = 0.8–2.2), mainly among men 70 or more years old (SIR = 1.8, 95% CI = 0.5–4.6).

As shown in Table 3, the risks for cancers of the intestine and kidney, as well as brain tumors, were elevated in both sexes, whereas the excesses of thyroid and bone cancers were limited to women. The overall risk of cancer was elevated throughout the study period, including 10 or more years after diagnosis of acromegaly (SIR = 1.4, 95% CI = 1.1–1.8), and risk did not vary by age at acromegaly diagnosis (data not shown).

Discussion

Our study confirmed the elevated risk of colorectal cancer previously reported among patients with acromegaly [4–9], and provides support to observations suggesting an excess of other forms of cancer [18–20]. With our larger sample size we were able to document elevated risks for cancers arising in all segments of the large bowel, as well as the kidney, thyroid, brain, and bone. The findings are noteworthy since acromegaly represents an extreme end of the spectrum of circulating IGF-1 levels, which have been correlated with the risk of various cancers in the general population [11–15].

GH is the primary stimulus for the production of IGF-1 and its main protein carrier in the blood, insulin-like growth factor binding protein-3 (IGFBP-3). The plasma levels of IGF-1 adjusted for IGFBP-3 have been related to the development of colorectal, prostate, and breast cancers, presumably as a result of its mitogenic and anti-apoptotic properties [21].

The excess risk of colorectal cancer and polyps reported in acromegaly is consistent with clinical observations in acromegaly relating the proliferative activity of colonic epithelial cells to circulating levels of GH and IGF-1 [22],

Table 3. Cancer incidence among acromegaly patients in Sweden and Denmark

Type of malignancy (ICD-7)	Men (6545 person-years)				Women (8179 person-years)			
	Obs.	Exp.	SIR	95% CI	Obs.	Exp.	SIR	95% CI
All cancers (140–209)[a,b]	80	54.2	1.5	1.2–1.9	97	64.0	1.5	1.3–1.9
Digestive system (150–159)	28	13.4	2.1	1.4–3.0	31	14.4	2.2	1.5–3.1
Stomach (151)	3	2.5	1.2	0.2–3.4	3	1.9	1.6	0.3–4.7
Small intestine (152)	2	0.2	8.1	1.0–29.3	1	0.3	3.9	0.1–21.7
Colon (153)	13	3.9	3.4	1.8–5.8	10	5.2	1.9	0.9–3.6
Rectum (154)	6	2.7	2.2	0.8–4.8	7	2.6	2.8	1.1–5.7
Liver (155.0)	1	0.7	1.4	0.0–7.70	2	0.5	3.6	0.4–13.2
Gall bladder (151.1)	0	0.3	0.0	0.0–11.9	2	1.0	2.1	0.2–7.4
Pancreas (157)	3	1.7	1.8	0.4–5.2	5	2.0	2.5	0.8–5.9
Lung (162)	8	7.3	1.1	0.5–2.2	6	3.5	1.7	0.6–3.7
Breast (170)	–	–	–	–	20	15.9	1.3	0.8–1.9
Corpus uterus (172)	–	–	–		4	3.8	1.1	0.3–2.7
Cervix (171)	–	–	–	–	3	1.9	1.6	0.3–4.7
Ovary (175)	–	–	–	–	2	3.5	0.6	0.1–2.1
Prostate (177)	13	10.3	1.3	0.8–2.2	–	–	–	–
Kidney (180)	7	2.0	3.5	1.4–7.1	5	1.8	2.9	0.9–6.6
Bladder (181)	3	4.3	0.7	0.1–2.0	0	1.7	0.0	0.0–2.2
Melanoma (190)	1	1.4	0.7	0.0–3.9	2	1.8	1.1	0.1–4.1
Non-melanoma (191)[c]	4	4.1	1.0	0.3–2.5	6	3.3	1.8	0.7–4.0
Brain and CNS (193)[d]	3	1.5	2.1	0.4–6.0	6	1.9	3.1	1.1–6.8
Thyroid (194)	0	0.2	0.0	0.0–17.6	3	0.6	5.0	1.0–14.7
Bone (196)	0	0.1	0.0	0.0–52.7	2	0.1	28.6	3.4–103.2
Connective tissue (197)	2	0.3	6.5	0.8–23.3	0	0.3	0.0	0.0–10.8
Hematopoietic (200–207)	6	4.0	1.5	0.6–3.3	3	3.8	0.8	0.2–2.3
Lymphoma (200–202)	3	1.9	1.6	0.3–4.7	3	1.8	1.2	0.3–4.8
Non-Hodgkin's lymphoma (200, 202)	2	1.6	1.3	0.2–4.6	3	1.6	1.9	0.4–5.5
All leukemia (204–207)	3	1.4	2.2	0.5–6.4	0	1.2	0.0	0.0–3.1

[a] Excluding 99 observed pituitary adenomas and the expected value for endocrine tumors in Sweden.
[b] Includes one esophagus, and three unspecified (Sweden), one lip, one other female genital, and three unspecified (Denmark).
[c] Includes squamous carcinoma in Sweden, and both squamous and basal cell carcinoma in Denmark.
[d] Includes benign and malignant tumors both in Sweden and Denmark.

and to an increased expression of proteins associated with cell proliferation and to a decrease in those related to apoptosis [10]. In addition, the risk of colorectal cancer in the general population has been linked to circulating levels of IGF-1 in case–control [11] and prospective studies among both men and women [12, 13]. The two- to three-fold excess risks of colorectal cancer reported in the highest prediagnostic categories of circulating IGF-1 in the prospective studies resemble the relative risks we and others have observed with acromegaly.

The elevated risk of small intestinal neoplasms in our study was confined to malignant carcinoid tumors which have been reported with multiple endocrine neoplasia type 1 (MEN-1), an inherited polyglandular syndrome that may involve the anterior pituitary and result in acromegaly [23]. However, we could not exclude the possibility in some cases that acromegaly was secondary to ectopic GH-releasing hormone secreted by a malignant carcinoid tumor [24].

The excess risk we observed for thyroid cancer is consistent with clinical reports of thyroid adenomas and carcinomas (papillary and follicular) in acromegaly [19]. The carcinogenic mechanism is unclear but may arise through the induction of goiter, which occurs excessively with acromegaly [25, 26] and predisposes to thyroid neoplasia [27, 28], a process that may be enhanced by the combined effect of thyroid stimulating hormone and IGF-1 on receptor sites [29]. It is also possible that thyroid and pituitary neoplasms are part of an underlying genetic syndrome such as MEN-1 or Carney complex [30], or that thyroid tumors result from radiotherapy to the pituitary [31]. The data in our study did not include information to evaluate these possible explanations.

It seems likely that the increased risk of brain tumors in our study was related at least partly to pituitary irradiation, which is usually given at doses of 40–50 Gy over 4–6 weeks [1, 18]. The findings are consistent with

the excess of brain tumors reported in some surveys of patients irradiated for pituitary adenoma [18, 32], as well as other groups of patients (*e.g.*, tinea capitis) receiving cranial radiotherapy [33, 34]. In some case reports of acromegaly, however, meningiomas have occurred in the absence of radiotherapy [35].

The increased risk we observed for kidney cancer has been noted previously in acromegaly [20], although based on small numbers, and may extend the range of tumors due to the mitogenic and anti-apoptotic stimulus of IGF-1 on receptor sites [36]. The high frequency of hypertension and obesity in acromegaly patients [37] may also contribute to the association, since both conditions are established risk factors for renal cell carcinoma [38, 39].

The increased risk of bone cancer in our study was based on only two cases (arising from the skull and long bone). The finding is interesting, however, in view of case reports of chondrosarcoma of the rib and osteosarcoma of the sacrum in acromegaly [40, 41], as well as the capacity of IGF-1 to stimulate osteosarcoma cell growth [42]. It is possible that the skull tumor in one patient was related to radiotherapy, since fibrous dysplasia of the skull with sarcomatous transformation has been reported with pituitary tumors treated with radiation [43].

Although an increased risk of breast cancer has been reported previously in small studies of acromegaly [6, 44], the slight excess in our study was not statistically significant. The modest excess we observed before age 50, however, is consistent with reports linking high serum IGF-1 concentrations to the risk of premenopausal breast cancer [15, 45]. In addition, we found that prostate cancer risk was slightly and non-significantly elevated, particularly for those 70 years of age or older. We are not aware of any reports linking prostate cancer to acromegaly, but long-term follow-up of these patients is needed since epidemiologic studies have related high plasma levels of IGF-1 to prostate cancer risk in the general population [14, 46, 47]. Although a positive association between lung cancer risk and IGF-1 levels has been reported in a case–control study [48], we found no significant excess in acromegaly, in accord with a recent prospective study of lung cancer which found no relationship to prediagnostic levels of IGF-1 [49].

Our population-based cohort study had the advantage of a virtually complete ascertainment of cancer cases and absence of recall bias, since diagnoses were derived from hospital discharge records and national cancer registries. However, review of medical records to confirm diagnoses and ascertain past medical and treatment (such as radiation) history was beyond the scope of this record-linkage investigation. Since it consisted of hospitalized cases with acromegaly, the study population may have included a disproportionate number of patients with more advanced disease or complications that required hospital admission. In addition, patients hospitalized for acromegaly may have had other medical conditions or exposures which predispose to cancer, but such information was not available to us. Finally, although our study is the largest to date of cancer risk in acromegaly patients, the sample size provided only limited statistical power to detect significant associations with less common cancer sites, such as multiple myeloma which has been noted in some clinical surveys of acromegaly [50].

In conclusion, our study revealed an elevated cancer risk in acromegaly, particularly for cancers of the intestines, kidney, thyroid, bone, and brain. Our findings underscore the need for careful medical surveillance of patients with acromegaly, and further studies of the IGF-1 system in the etiology of various malignancies.

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